ROLE OF MIFEPRISTONE AS AN ORALLY EFFECTIVE INDUCING AGENT, WITH CRITICAL EVALUATION OF THE DRUG ON PARTURITION MATERNAL AND NEONATAL OUTCOME IN PRIMI GRAVIDA AND MULTI GRAVIDA

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CHENNAI, TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**ROLE OF MIFEPRISTONE AS AN ORALLY EFFECTIVE INDUCING AGENT, WITH CRITICAL EVALUATION OF THE DRUG ON PARTURITION, MATERNAL AND NEONATAL OUTCOME IN PRIMI GRAVIDA AND MULTI GRAVIDA"** is a bonafide record work done by **Dr. M. SHAMEEMA BEGUM** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.D Branch II – Obstetrics & Gynaecology.

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DECLARATION

I **Dr. M. SHAMEEMA BEGUM** solemnly declare that the dissertation titled **"ROLE OF MIFEPRISTONE AS AN ORALLY EFFECTIVE INDUCING AGENT, WITH CRITICAL EVALUATION OF THE DRUG ON PARTURITION, MATERNAL AND NEONATAL OUTCOME IN PRIMI GRAVIDA AND MULTI GRAVIDA"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D degree Branch – II (Obstetrics & Gynecology) to be held in March 2010.

Place : Madurai **Dr. M. SHAMEEMA BEGUM**

Date :

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INTRODUCTION

Labour refers to the onset of effective uterine contractions leading to progressive effacement and dilatation of the cervix resulting in the expulsion of the fetus, placenta and the membranes.

According to Alec Turnbull (1976). "The spontaneous onset of labour is a robust and effective to mechanism which is preceded by the maturation of several fetal systems, and should be given every opportunity to operate on the own we should only induce labour when we are sure that we can do better."

The ideal method of induction of labour would mimic exactly the onset of spontaneous labour. Not surprisingly no method of induction currently available does this.

Induction is indicated when the benefits to either the mother or the fetus outweigh those of continuing the pregnancy.

The American college of Obstericians and Gynecologists (1999a) does not support elective induction, except for logistical reasons such as risk of rapid labour, the women lives a long distance from the hospital or for psycosocial indications.

Induction of labour has two important components, cervical ripening and stimulation of uterine contractions to achieve

dilatation of cervix and delivery of the fetus It is well recognized that the success of induction of labour, which ultimately aims at achieving vaginal delivery depends to a great extent on the favourability of the cervix or its readiness to go into labour. Agents used for cervical ripening may lead in the establishment of contractions to women with on unfavourable cervix.

Pharmacological methods like Prostaglandins (PGE_1 + PGE_2) relaxin and mechanical methods like membrane stripping, transcervical catheter, Hygroscopic cervical dilators etc are available for preinduction cervical ripening.

Mifepristone is a 19 nor – Steroid with a greater affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level. As a fall in the level of progesterone considered one of the important events in the onset of spontaneous labour. It therefore seems likely that this drug may be useful on induction.

A number of studies have looked at the efficacy of mifepristone on cervical ripening. There is a reduction in the induction delivery interval when induction is performed after mifepristone and a trend to a reduction in the rate of ceasarean section (Wing et al 2000).

AIM OF THE STUDY

1. To evaluate the efficacy and safety of oral mifepristone on induction of labour.
2. To evaluate the effect of this drug on parturition and neonatal outcome.
3. To critically evaluate the effect of this drug on primi gravida and multigravida.

REVIEW OF LITERATURE

INDUCTION OF LABOUR:-

It is defined as an intervention which is intended to artificially initiate uterine contractions resulting in the progressive effacement and dilatation of cervix. As part of the definition, it is assumed that this process will result in the birth of the baby by vaginal route.

Induction of labour is one of the most commonly practiced interventions in modern obstetrics.

Rates of Labour Induction:-

COUNTRY	RATE	SOURCE
USA	38%	MARTIN and associates 2003
England & Wales	18%	2001 b RCOG
Canada	19%	2000 Health Canada

HISTORY:-

The human race for centuries found reasons to interfere with pregnancy by trying to hasten its conclusion. Often this consisted of attempts to procure the abortion of unwanted pregnancies, but other more positive motives arose from the desire to relieve the mother of a life threatening pregnancy or to achieve mechanically more favourable vaginal delivery of a smaller premature baby through a constricted birth canal. Through time, as a better perception of fetal and maternal risks developed alongside more efficient methods of labour induction, the indications shifted more commonly to serve the interest of the fetus perceived to be in jeopardy.

The first reliable technique to be used widely in obstetric practice was amniotomy-artificial rupture of membranes. Although this procedure had probably been employed much earlier it first entered the medical literature in 1756. When Thomas Denman(1733-1815) of middle sex hospital of London wrote extrolling its virtues. As a result it became known within Europe as the ‘English method’.

Another mechanical method was devised in 1861 by Robert Barnes (1817-1907) of London, Using a hydrostatic bag placed through the cervix and filled with water with a view to labour induction. A similar approach was later taken by Camille champetier de Ribes (1848-1935) in Paris and by James Vorhees (1869-1929) in Newyork.

More than a century later modern obstetricians would follow the same principle using a foley catheter, but by now understanding that the modus operandi was the local release of prostaglandins.

Hind water rupture with Drew Smythe Catheter was introduced in 1931, but what gains in safety in terms of forewater preservation with reduced risk of Amniotic fluid infection and cord prolapse. It loses in efficiency when compared with forewater rupture.

Sir Henry Dale (1815-1968) made the first observation that posterior pituitary caused uterine contractions. Pitocin was first extracted from the posterior pituitary gland in 1906, and Blair– Bell described its application in the pregnant uterus in 1909.

In 1910, it was used for augmentation in cases of uterine inertia, but maternal deaths from shock were reported after

intramuscular injection of pitocin. Its use for induction was first reported by Theobald in 1952.

Oxytocin is the first polypeptide hormone synthesised by Du. Vigneaud and Coworkers, 1953. 'Physiological drip' (or) dilute intravenous infusion was introduced by Geoffrey Theobald pharmacologically sound approach of oxytocin titration was introduced by Alec Turnball and Anne –Anderson (1960)

Prostaglandin was first isolated from seminal fluid of monkeys, Sheep and Goat, by ulf von Euler at the Koralinska institute in stockholm in 1935. Elias corey Synthesised dinoprostone in 1970 at the Harvard University Bergstrom, Samuelson and vane jointly received the 1982 Nobel Prize for their discovery of prostaglandins.

RU -486 (or) mifepristone:-

The Compound was discovered by Researchers at Roussel uclaf of France in 1980 while they were studying glucocorticoid receptor antagonists. Etenne – Emile Baulieu recognized its anti progestrone activities and saw its potential for the induction of medical abortion the dug was first licensed in France in 1988, for

use in Combination with a Prostaglandian, under the name of mifegyne.

Indications for Induction of Labour :

1. For high risk pregnancies where there is risk to both the mother and the fetus

    Preclampsia and eclampsia

    Hypertension complicating pregnancy

    Renal disease complicating pregnancy

    Premature rupture of membranes and chorioamnionitis

2. Where there is increased likely risk to mother, if termination is not advocated

    1. Intrauterine death
    2. Abruptio placenta

3. Wherer the fetus is at risk

    1. Post term pregnancies
    2. Chronic placental insufficiency
    3. Rh isoimmunisation
    4. Maternal diabetes complicating pregnancy
    5. Previous unexplained still births
    6. Intrauterine growth restriction
    7. Anamalous baby

Contra indications : Absolute contraindications :

1. When vaginal delivery is contraindicated

    a) major degrees of cephalopelvic disproportion

    b) previous VVF repair

    c) pelvic tumour

    d) carcinoma cervix

    e) previous uterine surgery

    f) active herpes

2. Malpresentations cord prolapse or presentation

3. Placental abnormalities like vasa previa and type III and type IV placenta previa

Relative contraindications :

1. Grand multipara
2. Maternal heart disease
3. Abnormal foetal heart rate pattern

PRE INDUCTION CERVICAL RIPENING:-

The condition of the cervix is important to the Success of labour Induction, Cervical scoring was first described by Bishop in 1964. Various modifications of Bishops original score have been suggested and the most widely used is CALDER'S MODIFIED BISHOP'S SCIRE (1974).

Score	0	1	2	3
Dilatation (cm)	< 1	1-2	2-4	>4
Effacement (cm)	>4	2-4	1-2	>1
Station (cm)	-3	-2	-1,0	+1,+2
Consistency	Firm	Average	Soft	
Position	Posterior	Mid- Anterior		

A score of 9 conveys a high likelihood for a successful induction. For research purposes a Bishop score of 4 (or) less identifies as unfavourable cervix and may be an indication for cervical Ripening.

Cervical ripening is the process by which the cervix becomes soft, compliant & partially dilated. It is a fundamental process that must occur, if parturition is to progress smoothly.

Cervical ripening is due to a combination of Biochemical. Endocrine, mechanical and possibly inflammatory events.

It is believed that the increasing myometrial contractility, in the form of Braxton Hicks contractions seen with advancing gestation plays a vital role in the effacement of cervix, prior to the actual commencement of labour.

Structurally, the cervix is mainly composed of collagen, as opposed to the myometrium, which predominantly consists of

smooth muscle. There are four types of collagen in the human body – I, II, III, IV.

The cervix is predominantly composed of types I (66 percent) and III (33 percent). The firmness of the cervix in the non-pregnant state is mainly due to the properties of these collagen fibrils. These bundles in turn are embedded in ground substance consisting of proteoglycans.

The proteoglycans are made of a central core of proteins. which are linked to glycosaminoglycans, which are repeating disaccharide units composed of a hexosamine (glucosamine (or) galactosamine) and an uronic acid (glucuronic acid or iduronic acid) residue.

In the cervix, the main glycosaminoglycans are dermatan sulphate and chondroitin sulphate, both of which are highly negatively charged and hydrophobic. Hence, they repel water and are responsible for the firmness of the cervix. Moreover, by interacting with the central protein core as well as among themselves, glycosaminoglycans facilitate the optimum orientation of the collagen fibrils, enhancing, the mechanical strength of the cervix.

Towards term, the glycosaminoglycan Concentration alters and the dermatan and chondroitin sulphate are replaced by hyaluronic acid, which has different physio chemical properties.

Hyaluronic acid is hydrophilic and imbibes water Accumulation of water within the substance of the cervix destabilises the collagen fibrils, contributing to cervical ripening.

The water content of the human cervix increases from 80 percent in the non- pregnant state, to 86 percent in late pregnancy (Liggins 1978; Uldbjerg et al 1983a). The accumulation of water in between the collagen fibrils has a scattering or dispersing effect, resulting in reduced mechanical strength.

Collagenase & leukocyte elastase levels are found to increase with advancing gestation and are associated with progressive decline in the concentration of cervical collagen. (Uldbjerg et al 1983 b).

The mature collagen, which has many crosslinks that are responsible for its tensile strength, is replaced by an immature collagen which has a few cross links.

Ganstrom et al (1991) have shown that the insufficient remodelling of collagen during pregnancy is an independent factor that results in labour.

METHODS OF CERVICAL RIPENING:-

There has often been an attempt to make a distinction between women who are undergoing cervical ripening and women who are being formally induced. This tendency is artificial, as in all the intention is to artificially stimulate the onset of labour.

Women undergoing cervical ripening are simply those in whom there is an unfavourable cervix and where the indication allows the greater time expected for induction to establish active labour.

As the first stage of labour is a seamless progression from the latent into active phase, so induction is a progression from cervical ripening through to the onset of contractions.

Agents used for cervical ripening may lead to the establishment of contractions in women with an unfavourable cervix. Many agents can be used in both women with high and low cervical scores, albeit with a different expectation of the time likely before delivery will be achieved.

Non-Pharmacological methods:-

Sexual intercourse, herbal remedies, castor oil, enemas, acupuncture, baths. No Study has shown any proven benefit of these therapies for induction of labour.

Sweeping of membranes:-

It is an old method of inducing labour described by Hamilton in 1810.

Mc Colgin and Collegues (1990) reported that two thirds of women who underwent stripping entered spontaneous labour within 72 hours.

The procedure of membrane sweeping causes an increase in the levels of Prostoglandin F_2 alpha (Mc colgin et al 1993).

Bouvelian and colleagues (1999) – Sweeping the membranes as a routine at term reduced the chances of pregnancy progressing beyond 41 weeks and reduce the need for induction of Labour from 36 to 21%.

Mechanical methods:-

Intrauterine Extraamniotic Foley Catheter with bulbi inflation to 30ml - Rapid improvement in Bishop Scores and shorter labours (Sherman and Colleagues 1996).

Bujold and coworkers (2004) reported a lower incidence of success when induction by Foley catheter was compared with that by oxytocin – 56 versus 78 percent.

Extra – amniotic saline infusion (EASI):-

Abromovici and coworkers (1999) reported that 85 percent of those induced by catheter infusion delivered within 24hrs compared with 55 percent of those given misoprostol.

Mullin and associates (2002) reported that mean induction to delivery interval was shorter in the catheter plus oxytocin group.

Hygroscopic cervical dilators:-

Guinn and co-workers (2000) reported a longer induction to delivery interval with cervical dilators plus oxytocin compared with that of EASI Plus oxytocin.

The use of hygroscopic dilators appear to be safe, although anaphylaxis has followed laminaria insertion (Cole and Neek 2000)

The attraction of dilators is their low cost and ease of placement and removal.

As mechanical methods are believed to facilitate ripening by causing local release of Prostaglandin their use has been superseded by administration of local prostaglandin in most units.

Pharmacological methods:-

Prostaglandins:-

Prostaglandins probably induce cervical ripening by producing vasodilatation of the cervical blood vessels and increased extravasation of the neutrophil (Rajabi et al 1988).

The extravasated neutrophils then degranulate and release large quantities of collagenases and proteases which degrade cervical collagen and soften the structure of the cervix (Rajabl et al 1988).

Prostaglandins act synergistically with interleukin 8 (IL -8) to stimulate the fibroblasts to produce hyaluronic acid (Ogavia et al 1998) which in turn alters the composition and structure of the cervix.

This effect on the cervix along with uterotonic effects of prostaglandins and other uterotonics on the uterus enables the cervix to efface and dilate during labour to allow parturition.

Prostaglandin E_2

Compared to the placebo, the induction of labour with a vaginal prostaglandin gel has been consistently shown in several trials to be associated with and increased Bishop score and a

reduced incidence of ceasarean section (Brennand and Green 1998).

The United Kingdom's national institute for clinical Excellence (NICE) Guidelines on the induction of labour recommends that prostaglandin E_2 should be used in preference to oxytocin for the induction of labour in women with intact membrane regardless of their parity or the ripeness of the cervix.

In women with term prelabour rupture of membranes Prostaglandin (dinoprostone PGE_2) and oxytocin are equally effective for the induction of labour, regardless of their parity (or) the state of the cervix (Tan and Hannah 2000).

Prostaglandin E_1:-

1. Misoprostol use may decrease the need for oxytocin achieve higher rates of vaginal delivery within 24hrs of induction and reduce induction – delivery intervals. (Sanchex – Ramos and colleagues, 1997).

2. The committee on obstetrics and gynecologists (1999 b) recommended the use of a 25ug intravaginal dose.

3. Data from the United Kingdom Cochrane centre support these recommendations. But the investigators cautioned that

increased uterine hyperstimulation with adverse fetal heart rate changes was of concern (Hotmeyr and associates, 1999).

4. IN DECEMBER 2000, the American college of obstetricians and Gynecologists reaffirmed its recommendation for use of the drug because of proven safety and efficacy.

5. A 25 microgram dose was found comparable to dinoprostone gel (Van Gemund and associates, 2004).

OXYTOCIN:-

In modern obstetric practice oxytocin is more commonly used in combination with amniotomy making it unsuitable for use in women who have cervical scores below 6.

When compared to induction with prostaglandins evidence suggests that oxytocin induction is associated with a lower chance of delivery within 24hours.

In women with an unfavourable cervix, induction with oxytocin was associated with higher rates of ceasarean section.

Lower dose regimens are recommended with starting doses of 1-2 milli units / min, increased at intervals of not less than 30 minutes. The maximum dose is the minimum needed to maintain a

contraction frequency of 3-4 in ten minutes (or) an absolute maximum of 32 milli units per minute.

RELAXIN:-

Relaxin has been used both vaginally and intracervically to induce labour but studies have failed to show any benefit compared to prostaglandin (Kelly 2002b).

Hyaluronidase and estrogen are of historical interest only (Thomas et al 2001).

RU 986 OR MIFEPRISIONE:-

It is a derivative of 19 nor progestin norethindrone containing a dimethyl – aminophenol substituent at the 11 beta position it effectively competes with both progesterone and glucocorticoids for binding to their respective receptors.

This antiprogestin has been studied extensively for preinduction cervical ripening at term.

a. A 200mg dose given orally for 2 days, 48hrs before the formal induction Engdman and associates (1992) reported that mifepristone is a safe efficient and suitable induction agent for initiation of labour at term.

b. Single dose of 400mg mifepristone was effective for cervical ripening and reduce the induction delivery interval (Giacalone PL: Targosz V : Laffargue : Boog G: faure JM)

c. Induction of labour is facilitated in term women with prior ceasarean section by the use of mifepristone. This induction agent appears safe and useful with no adverse effect on the fetus or mother (Lelaider c: Barton C: Benifla JL, Fernandaz H : Bourget P: Frydman R: (1994).

d. Single dose of 400 milligram mifepristone (for Preinduction cervical ripening in women with an unripe cervix.) is a simple and effective treatment (Stenlund PN: Erkman G: Aedo AR: Bygdeman N 1999).

e. Mifepristone had a modest effect on cervical ripening when given 24hrs before labour induction, appearing to reduce the need for misoprostol and oxytocin compared with placebo (Wing Da: Fassect Mj: Mishell DR 2000).

Amniotomy:-

Artificial rupture of membranes can be used to induce labour: but implies a commitment to delivery. The main disadvantage of

amniotomy when used for induction is the unpredictable and occasionally long interval, to the onset of contractions.

There is an increased incidence of chorioamninitis (23 percent) and cord compression patterns (12 percents) with early amniotomy.

RISKS OF INDUCTION OF LABOUR:-

Increase in ceasaren Section rate:

The risk of ceasarean section increased nearly threefold in primigravid women (11.8% Vs 27.9%) and doubled in multigravid women (3.4% Vs 8.5%) who were induced compared to those labouring spontaneously (RCOG 200 lb).

Uterine Hyper Contractility:-

Uterine hypertonus is defined as a single uterine contraction that lasted 2 or more minutes.

Tachysystole is defined as at least 12 contractions in 20 minutes. Hyperstimulation is defined as either hypertonus (or) tachysystole associated with abnormal FHR pattern.

Misoprostol was associated with significantly increased risk of tachysystole or hyper stimulation when compared with PGE 2 gel (WING and Coworkers 1995a, 1995b).

Induced labour is associated with on increased risk of postpartum hemorrhage.

Prolonged induction is associated with a small increase in the risk of infectious morbidity with an estimated 10% incidence noted after 40hrs of induction (Bahn et al 1998).

Oxytocin induction has been reported to increase the risk of neonatal Hyperbilirubinemia.

Iatrogenic prematurity occurs inadvertently and a review of the gestational age prior to induction is essential.

Failed induction:

Defined by Duff et al (1984), as the failure to enter to active phase of labour, after twelve hours of regular uterine contractions. Failed induction, is diagnosed when, a patient who was induced, does not deliver vaginally in the absence of fetal distress, with acute events like abruption or cord prolapse, and failure to progress due to malposition and or if the patient has not entered the active phase of labour despite adequate management for twelve hours (Arulkumaran et al 1985).

MIFEPRISTONE

INTRODUCTION:-

Mifepristone was originally designed by the French pharmaceutical company (Romainville, France) as a glucocorticoid antagonist and was only serendipitously found to have antiprogesterone effects. Many of its potential actions still under research.

Pharmacodynamics:-

Mifepristone is a 19 nor-steroid with potent competitive antiprogestational and significant antiglucocorticoid and anti androgenic activity.

At the molecular level, the most important features are high binding affinity to the receptor, interaction of the phenylaminodimethyl group in the 11 beta position with a specific region of receptor pocket and mifepristone induced transconformation differences in the ligand binding domain. It renders the mifepristone – progesterone receptor complex inactive and unable to promote transcription of cellular DNA.

Mifepristone binds with very high affinity (2-10 times that of progesterone) to the progesterone receptors. In the absence of progesterone, however, mifepristone can act as a partial agonist.

Endometrial Effects:-

Mifepristone blocks the effects of natural Progesterone on the endometrium and decidua. This leads to degeneration and shedding of the endometrial lining thereby preventing or disrupting implantation of the conceptus.

Mifepristone also increases both uterine production of Prostaglandins and uterine sensitivity to the contractile effects of prostaglandins.

Mifepristone acts directly on the uterine muscle through an entirely separate mechanism, perhaps by increasing gap junctions in the myometrium.

Tissue culture studies have shown that mifepristone continues to display procontractile effects on the uterus even when the effects of Prostaglandins are neutralised by treatment with indomethacin.

CERVIX: Mifepristone stimulates the release of nitric oxide and the expression of cervical iNos in cervical cells of women in early pregnancy (Human reproduction 2006 21(8); 2180-2184).

Mifepristone induced a decrease in the cervical tensile strength that was associated with a decrease in the collagen organization. Mifepristone led to collagen fragmentation with a significant decrease in fibril length and diameter, although fibril bundling remained unaffected. Matrix metalloproteinase-2 expression increased after the administration of mifepristone. (American Journal of obstetrics and gynecology, volume 194, Issue 5, Pages 1391-1398).

Gonodotropic effects:-

The effects of mifepristone on the Hypophysical – ovarian axis have also been studied and reported in the literature. Mifepristone has differing effects on the usual hormonal milieu when it is administered during the menstrual cycle.

Given during the follicular phase, its antiprogestin action results in attenuation of midcycle LH Surge from pituitary -→slowing of follicular development and delay or failure of ovulation.

Adrenocortical effects:-

Mifepristone has antiglucocorticoid effects by binding to glucocorticoid receptors with on affinity that is 2-3 times that of

Dexamethasone. It interferes with cortisol binding to tissues in the hypothalamus. This blocks normal negative feedback mechanisms and causes a compensatory increase in serum levels of both cortisol and corticotropin.

Mifepristone binds to cortisol receptors in the periphery and therefore blocks the effects of circulating cortisol in target tissues. Higher doses of mifepristone are needed to produce this antiglucocorticoid effect as opposed to an antiprogestin effect because blockade in the periphery is opposed by increased cortisol and corticotropin secretion.

No Reports of clinically significant relative cortisol deficiency have been reported when it has been used as an antiprogestin, even with long term use of mifepristone for several weeks.

Mifepristone has almost no affinity for estrogen and mineralocorticoid receptors.

Pharmacokinetics:-

Mifepristone has a bioavailability of 70% after oral administration, peak plasma concentrations are reached in 1-2 hrs after a single oral dose. It has a half life of approximately 20-30 hours

The pharmacokinetics of mifepristone are non-linear. Serum drug concentrations increase progressively after oral doses from 50- 100mg, but no further increases occur after doses of 100-200mg. This is partly due to progressive saturation of Alpha-1 acid glycoprotein, the serum binding protein for mifepristone.

The unbound mifepristone is quickly metabolized in the liver by a two step process, demethylation and hydroxylation, with metabolites detectable in plasma about 1 hr after oral ingestion. The concentration of metabolites increases in a dose dependent manner. Metabolites bind to progesterone receptors with an affinity of 10-20% that of the parent compound. These metabolites probably contribute little to the pharmacologic effect of mifepristone.

Both mifepristone and its metabolites are excreted primarily in the feces via the biliary system. Little is cleared by kidneys.

Mifepristone crosses the placenta. The maternal – fetal ratio in plasma is approximately 9:1.

Clinical Uses:-

1. **First Trimester abortion:-**

Mifepristone softens and dilates the cervix, causes decidual necrosis, increases prostaglandin release, increases uterine contractions and enhances uterine sensitivity to administered prostaglandins.

	FDA approved protocol	**Other evidence based regimens**
Mifepristone dosage	600mg (Day1)	200mg (DAY1)
Misoprostol dosage	400mg PO	400mg PO (or) 800mg PV
Gestational limit	<49 days	<63 days
Location of misoprostal administration	At clinic	At clinic / home
Timing of misoprostol administration	DAY 3	DAY 2,3,(or)4
Timing of initial follow up	DAY 14	DAY 4-14
No of clinical visits required	3(or)more	>2

67% of women will have a complete abortion within 4 hrs of using misoprostol, 9 of will have complete abortion within 24hrs of using misoprostol.

Preoperative cervical preparation before vaccum aspiration:-

200mg mifepristone administrated, 36 hrs before vaccum aspiration is a highly effective cervical priming agent. (BJOG Volume 98 issue to pages 1025-1030).

Induction of second trimester abortion:-

Mifepristone with prostaglandins either misoprostol (or) germprost is a safe and effective method which reduces induction –abortion interval (BJOG Volume 100: issue 8, page 758-761)

Intra uterine demise (21weeks to 40weeks):-

Wagarrachi et al (2002) – mifepristone 200mg following by 200mg misoprostol if gestational age is less than 34 weeks, First dose of misoprotol was given 36 hrs after oral mifepristone, and then repeated every 4^{th} hourly orally upto four doses.

There were no adverse maternal events and this regimen is safe and effective.

Mifepristone is a safe and efficient induction agent for initiation of labour in women at term (Frydmen et al 1992).

Emergency contraception:-

10mg mifepristone administered within 5 days of sexual intercourse is an effective contraceptive with an acceptable profile of side effects.

Fibroid :

Progestrone binds either PR-A / PR-B, mifepristone exerts its effects mainly through PR-A which is found in lieomyomas in greater amounts than PRB, mifepristone decrease lieomyoma volume by approximately half. (Eisinger 2003).

Endometriesis:-

50mg mifepristone daily for 3 months causes 55% regression of endemetriotic implants.

Neuropsychiatric disordess:-

Mifepristone is a potent glucocorticoid and progesterone receptor antagonist. The pathophysiology of number of neuropsychiatic disorders implicates abnormalities in glucocorticoid function. These include mood disorder such as psychiatric major depression, and bipolar depression. In addition cognitive disorders such as Alzheimer's disease might also partially mediated by abnormalities in the HPO axis. Preliminary studies

suggest that mifepristone might have a role in the treatment of number of neuro psychiatric disorders (Trends in Endocrinology and metabolism volume 17, issue 10, Dec.2006).

Unresectable meningioma:-

As progesterone receptors are expressed in meningiomas, partial response or prolonged stabilisation was seen in 47% following T.mifepristone 200mg daily for 6-12 months.

(PEREZ and BRADY'S Principles of radiation oncology, Page 744).

Breast cancer:-

Mifepristone effectively reversed P-glycoprotein and MDR-associated protein in mice thymoma cells, mifepristone induces growth arrest and active cell death of the antiestrogen resistant breast cancer cells.

The combination of antiestrogen and antiprogestin reduces the emergence of antiestrogen resistant breast cancer cells and ultimately improve the therapeutic index of antiestrogen therapy.

Cushing Syndrome:-

Larger doses of mifepristone 5 to 22 mg/kg must be used to obtain antiglucocorticoid effect.

Prostate Cancer:-

Mifepristone is an effective inducer of apoptosis and useful in androgen independent prostate carcinoma.

HIV:-

Mifepristone has antiretroviral effect by inhibiting the Vpr induced transactivation of the HIV–LTR in dose dependent manner.

IVF:-

Mifepristone is effective for the prevention of Premature LH surge in women undergoing controlled ovarian hyperstimulation for IVF, however endometrial receptivity status requires further evaluation before this drug can be considered as a new alternative to GNRH agonist (or) antagonist.

Contraindications:-

(I) Hemorrhagic disorders (or) concurrent anticoagulant therapy.

(II) Inherited Porphyrias

(III) Chronic adrenal failure

(IV) History of allergy to mifepristone

(V) Concurrent long term corticosteroid therapy (or) recent therapy with corticosteroid.

(VI) Chronic medical disorders.

(VII) Age more than 35years

(VIII) Smokers (>10 cigarettes /day).

Drug interactions:

On the basis of this drug metabolism by CYP 3A4, Ketoconazole, itraconazole, erythromycin and grape fruit juice may inhibit its metabolism. Rifampin, dexamethasone and certain anticonvulsants like phenytoin, phenobarbitone and carbamazepine may induce mifepristone metabolism.

Side effects;-

Adverse Reactions associated with single dose of mifepristone are nausea, vomiting, diarrhea, dizziness, headache, fever, warmth and chills.

Long term administration of mifepristone may cause anovulatary amenorrhea, hot flushes, transient thinning of hair and weigh loss.

MATERIAL AND METHODS

This prospective clinical trial was carried out in the Department of obstetrics and gynaecology, Government Rajaji Hospital Madurai, during the period of May 2009 to November 2009.

The purpose of the study was to evaluate the safety and efficacy of mifepristone as an orally active inducing agent in women with unfavourable cervix at term (Bishop score < 4).

Inclusion Criteria :

i) Singleton live pregnancy in cephalic presentation.

ii) Gestational age more than 38 weeks

iii) Bishop score < 4

iv) Reactive FHR pattern

v) Intact membranes

vi) Maternal age > 18 years and < 35 years

vii) Term and post term pregnancies with no contraindications for vaginal delivery.

viii) No contraindications for mifepristone and prostaglandin E2gel

ix) Primi gravida and second gravida

Exclusion Criteria :

i) Multiple pregnancy

ii) Malpresentations

iii) Cephalopelvic disproportion.

iv) Premature rupture of membranes

v) Bishop score > 4

vi) Non reactive FHR pattern

vii) Maternal age < 18 years and > 35 years

viii) Previous H/o ceasarean section or uterine surgery

ix) Contraindications for vaginal delivery

x) Contraindications for mifepristone and prostaglandin

xi) Chronic medical disorders

xii) Parity > 2.

This study contained 50 women who were inpatients in the labour and delivery units of Government Rajaji Hospital, Madurai.

On admission, a detailed history was taken. Complete general and obstetric examination was carried out. Under strict aseptic precautions, vaginal examination was done. Bishop's score was assessed.

Gestatational age was determined by the date of the last menstrual period preceded by regular cycles and confirmed by ultrasonography no later than 20 weeks.

Routine obstetric scan for fetal maturity and well being was done. Once the inclusion criteria were fulfilled, the patient was counselled and written informed consent obtained.

Treatment Schedule :

On Day 1, after assigning the initial Bishop's score, 200 mg of T. mifepristone was given orally. After 24hrs, Bishop's scores were reassessed. If Bishop's scores were less than 6 and reactive FHR pattern, second dose of mifepristone 200 mg orally was given on Day 2. If Bishop scores were more than 6, labour was augmented with oxytocin.

After 48 hrs of initial treatment, if Bishop's scores were less than 6 and reactive FHR pattern induction with PGE2 gel was done on 4^{th} day. If Bishop's scores were more than 6, labour was augmented with oxytocin. Once in active labour, patients were managed routinely.

Monitoring of the patients :

From the start of induction with mifepristone, uterine activity and fetal heart rate were monitored clinically. Frequency and duration of contractions were monitored by abdominal palpation. Fetal heart rate was monitored by using Pinard's fetoscope, once in every 30 minutes till the onset of labour pains, once in 15 minutes during the first stage, once in 5 minutes during the second stage. The pulse rate, blood pressure and temperature were recorded every hour. Progress was monitored by using WHO partogram during active stage. If the membranes were ruptured, vaginal examination was done to assess the Bishop's score and colour of liquor was noted. If any maternal side effects like nausea, vomiting, fever, chills etc were noted. If any FHR abnormality was present, it also noted

The outcome was assessed by

i) Induction – delivery interval
ii) Duration of 1^{st} and 2^{nd} stage
iii) Intrapartum complications like uterine contractility abnormalities, meconium passage, abnormal FHR pattern
iv) Mode of delivery

v) Neonatal outcome Apgar 1 minute & 5 minutes, NICU admission)

vi) Need for oxytocin

vii) Need for prostaglandin E_2 gel

viii) Maternal side effects

Success of Induction was assessed by

i) Patient who delivered vaginally within 48 hrs of the start of induction. or

ii) Bishop's score of more than 6 at the end of 48 hrs.

Failure of Induction :

i) Bishop's score of 6 or less than 6 at the end of 48 hrs. or

ii) Patient who underwent caesarean section

Statistical Tools :

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological information package. (EPI 2008).

Using this software frequencies, percentages, means, standard deviations, Chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

Table 1

Age in years	Primi (no=30)		Multi (no=20)		Total	Total
	No.	%	No.	%	No.	%
<20	3	10	3	15	6	12
21-25	22	73.3	11	55	33	66
26-30	5	16.7	6	30	11	22
>30	-	-	-	-	-	-
Total	30	100	20	100	50	100
Mean age S.D/	23.4 2.3		24.0 2.4		23.7 2.3	
P	0.3631 (Not significant)					

Among the 30 primigranda selected, 22 (73.3%) were between 21-25 years of age, 5(16.7%) were between 26-30 years, and 3 (10%) were between 18-20yrs. None were more than 30years.

Among the 26 multigravida selected, 11(55%) were between 21-25 years, 6 (30%) were between 26-30 and 3(15%) between 18-20 years. None were more than 30 years.

TABLE 2

GRAVIDITY

GRAVIDITY	No.	%
PRIMI	30	60%
MULTI	20	40%
TOTAL	50	100

Among the 50 patients selected 30 (60%) were primigravida and 20 (40%) were multigravida.

TABLE 3

INDICATION FOR INDUCTION

S.No	INDICATION	PRIMI (No= 30)		MULTI (NO=20)		TOTAL No.	TOTAL %
		No.	%	No.	%	No.	%
1	Postdatism	27	90	18	90	45	90%
2	Pre eclampsia	3	10	2	10	5	10%
	Total	30	100	20	100	50	100

The major indication for induction was for postdatism which accounted for 90% (45) of the study group. The next indication was for pre eclampsia accounted for 10% (5) of the study group (Both in Multi & primigravida).

TABLE 4

BISHOP'S SCORE AT THE START OF THE STUDY

SCORE	PRIMI		MULTI		TOTAL No.	TOTAL %
	No.	%	No.	%	No.	%
0	5	16.7	-	-	5	10
1	2	6.7	3	15	5	10
2	19	63.3	13	65	32	64
3	4	13.3	4	20	8	16
TOTAL	30	100	20	100	50	100
Mean Score	1.73		2.05		1.86	
S.D	0.91		0.6		0.81	

'P' 0.303 (Not Significant)

5 Primi and none of the multi that is a total of 10% had a bishop's score of 0. 2 primi and 3 multi that is a total of 10% had a score of '1' while 19 Primi and 13 multi that is a total of 64% had a score of '2' while 4 primi and 4 multi that is a total of 16% had a score of 3 at the beginning of the study.

Of the 30 primigravida, 26 (36.7%) had a Bishop's Score of <2 while 4 (13.3%) had a bishop's score of '3'

Of the 20 multigravida ,16 (80%) had a Bishop's score of ≤ 2 while 4(20%) had a score of '3'

TABLE 5

Number of Doses (mifepristone) Required

No of Doses	PRIMI		MULTI		TOTAL	TOTAL
	No.	%	No.	%	No.	%
Single close on DAY 1	21	70	19	95	40	20
Two dose on DAY 1 & 2	9	30	1	5	10	20
Mean doses	1.3		1.05		1.2	
S.D	0.47		0.22		0.4	
'p'	0.0321(significant)					

A total of (80%) that is 21 Primi and 19 multi (95%) required single dose. While (10%) 9 Primi and 1 (15%) that is a total of 20% required two doses (30%).

Of the 30 primigravida, 21 (10%) required single dose and 9 (30%) required two doses.

Of the 20 multigravida 19 (95%) required single dose and 1 (5%) required two dose.

There was statistically significant difference in the no. of doses (mifepristone) required for Induction between primi gravida and multigravida (p=0.0321)

TABLE - 6

OXYTOCIN FOR AUGMENTATION

OXYTOCIN	PRIMI		MULTI		TOTAL	TOTAL
	No.	%	No.	%	No.	%
REQUIRED IN	5	16.7	-	-	5	10%
NOT REQUIRED	25	83.3	20	100	45	90%
'P'	0.0723 (Not significant)					

Of the 30 primigravida, 5 (16.7%) required oxytocin for augmentation but none of the multigravida required oxytocin for augmentation, that is a total of 10% required oxytocin for augmentation.

However, there was no statistically significant difference in the requirement of oxytocin between primigravida and multigravida.

TABLE 7

PGE2 GEL FOR INDUCTION ON DAY 4

PGE2 GEL	PRIMI		MULTI		TOTAL	TOTAL
	No.	%	No.	%	No.	%
REQUIRED IN	2	6.6	-	-	2	4
NOT REQUIRED	28	93.4	20	100	48	96
'P'	0.3551 (Not significant)					

Two primigravida (6.6%) and none of the multigravida, that is a total of 4% required PGE_2 gel for induction on DAY 4.

TABLE 8

DURATION OF THE 1ST STAGE OF LABOUR

TIME (HOURS)	PRIMI		MULTI		TOTAL	TOTAL
	No.	%	No.	%	No.	%
<6	1	8.4	4	20	5	10.2
6-8	6	20.7	11	55	17	34.7
8-10	9	31	4	20	18	26.5
10-12	7	24.1	1	5	8	16.3
12-14	8	10.8	-	-	3	6.1
14-16	3	10.3	-	-	3	6.1
TOTAL	29	100	20	100	49	100
Mean duration	9.79 3.71		6.98 1.61		8.64 2.7	

‘p’	0.0001 Significant

1 of the 30 primigravida, was excluded, while calculating the first stage duration, as she was taken up for LSCS for fetal distress.

A total of 10.2%, that is 1 primi 4 multigravida, had a first stage duration of less than 6 hours. A total of 87.8% that is 23(79.2%) primi and 20 multi (100%) had a first stage duration of less than 12hrs. Only 6 Primi (20.2%) and none of the multi (0%) that is a total of 12.2% had first stage duration more than 12 hours. The mean first stage duration was 8.64 hours.

Therefore first stage duration less than 12hrs was more in multigravida than in primigravida (100% vs 19.2%)

The mean duration of first stage of labour for primi gravida was 9.79hrs and for multigravida was 6.98 hours

The mean duration of first stage was less in multigravida which was statistically significant (p=0.0001).

TABLE 9

DURATION OF THE 2nd STAGE OF LABOUR

TIME (HOURS)	PRIMI		MULTI		TOTAL No.	TOTAL %
	No.	%	No.	%	No.	%
0 – 10	5	17.2	7	35	12	24.5
10 – 20	16	55.2	12	60	28	57.1
20 – 30	7	24.1	1	5	8	16.4
>30	1	3.5	0	0	1	2.0
Total	29	100	20	100	49	100
Mean Duration	16.06		10.78		18.91	
S.D.	7.29		2.78		6.34	
‘p’	0.0009 significant					

1 of the 30 primigravida was excluded while calculating the second stage duration as she was taken up for LSCS for fetal distress.

The majority of the patients, that is 98% which consisted 28 (96.5%) primi and 20 (100%) multigravida had second stage duration of less than 30 minutes. Only 1 (3.5%) primigravida and none of the multigravida that is a total of 2% had second stage duration of more than 30 minutes. The mean second stage duration was 13.9 minutes.

The mean second stage duration in primi was 16.06 minutes and in multi gravida was 10.78 minutes. Therefore, the mean second stage duration was less in multigravida than the primigravida. (p=0.0009 - statistically significant).

TABLE 10

(INDUCTION - DELIVERY INTERVAL)

Time of Hours	PRIMI		MULTI		TOTAL	TOTAL
	No	%	No	%	No	%
<8	-	-	3	15	3	6.38
8-12	-	-	12	60	12	25.53
12-16	9	35.33	3	15	12	25.53
16-20	4	19.81	1	5	5	10.63
20-24	3	11.11	-	-	3	6.38
24-28	4	14.81	-	-	4	8.5
28-32	1	3.70	-	-	1	2.12
32-36	2	7.4	1	5	3	6.38
36-40	1	3.70	-	-	1	2.12
>40	3	11.11	-	-	3	6.38
TOTAL	27	100	20	100	47	100
Mean duration	23.11		11.48		18.41	
S.D.	11.9		5.41		11.41	
'p'	0.0001 (significant)					

Of the 30 primigravida, 3 cases were excluded while calculating induction – delivery interval. Among the three one was taken up for LSCS for fetal distress, the remaining two required PGE_2 gel induction on day 4 as their bishop Score's remained unfavourable

A total of 74.45% that is 16 (59.25%) primi and 19(95%) multigravida delivered within 24hrs. A total of 17.01% that is 1(25.9%) primi and 1(5%) multi delivered within 36 hrs. Only 4 (14.7%) primi but none of the multigravida, that is a total of 9.5% delivered after 36 hrs of induction, mean induction delivery interval was 18.61 hrs.

The mean induction delivery interval in primi was 23.7 hours and in multigravida was 11.48 hrs. Therefore the induction delivery interval was shorter in multigravida (p=0.001– statistically significant.)

TABLE - 11

INTRAPARTUM COMPLICATIONS

Intrapartum Complications		PRIMI		MULTI		TOTAL	TOTAL
		No	%	No	%	No	%
Uterine Contraction Abnormalities	Hypertonus	0	0	0	0	0	0
	Tachysystole	0	0	0	0	0	0
	Hyperstimulation	0	0	0	0	0	0
Fetal heart rate abnormalities		6	20	1	5	7	14
Meconium Passage	Thin	5	16.6	0	0	5	10
	Thick	1	3.3	0	0	1	2

None of the study population had uterine contraction abnormalities.

A total of 14% that is 6 primi (20%) and 1(5%) multi had FHR abnormalities.

A total of 10%, that is 5 (16.6%) primi had thin meconium stained liquor and 1(3.3%) primi had thick meconium stained liquor. But none of the multi had meconium stained liquor.

Table – 12

Mode of Delivery

Mode of Delivery		PRIMI		MULTI		TOTAL	TOTAL
		No	%	No	%	No	%
Labour Natural		24	80	20	100	44	88
Instrumental Delivery	Outlet forceps	5	16.7	0	0	5	10
	Midcavity forceps	0	0	0	0	0	0
	Vaccum delivery	0	0	0	0	0	0
LSCS	Failed Induction	0	0	0	0	0	0
	Fetal distress	1	3.3	0	0	1	2
		30	100	20	100	50	100

Unassisted vaginal delivery ensued in a total of 88% that is in 24 (80%) primi and 20 (100%) multigravida.

None of the multigravida required instrumental delivery or underwent LSCS.

Only 5 primi (16.6%) required instrumental delivery (in the form of outlet forceps delivery) that is a total of 10%.

Only 1(3.3%) primi was taken up for LSCS for fetal distress, that is a total of 2%.

Table – 13

Maternal Complications

Complications	PRIMI		MULTI		TOTAL	TOTAL
	No	%	No	%	No	%
Nausea vomiting	2	6.7	1	5	3	6
Fever	4	13.3	0	0	4	8
Puerperal sepsis	0	0	0	0	0	0
Rupture uterus	0	0	0	0	0	0
Postpartum hemorrhage	0	0	0	0	0	0
Requirement for blood transfusion	0	0	0	0	0	0

The incidence of minor maternal complications in the form of nausea and vomiting were seen in a total of 6%, that is in 2 (6.7%) primi and 1 (5%) multigravida. Fever was seen in a total of 4 (8%) that is in 4(13.3%) primi and none of the multigravida

Major maternal complications like post partum hemorrhage and requirement for blood transfusions, rupture uterus or puerperal sepsis were nil in this series of 50 patients both in multi and in primi gravida showing the safety and efficacy of the regime.

Table - 14

Neonatal Outcome

Parameters	PRIMI		MULTI		TOTAL	TOTAL
	No	%	No	%	No	%
Mean birth weight in kgs	2.9		2.81		2.86	
5 min Apgar < 7	4	13.3	1	5	5	10
Meconium Aspiration syndrome	1	3.3	Nil	0	1	2
Neonatal I.C.U. admission	6	20	1	5	7	14
Neonatal mortality	0	0	0	0	0	0

5 minute Apgar score less than 7 was seen in a total of 5 (10%) that is in 4 primi (13.3%) and 1(5%) multigravida

The incidence of meconium Aspiration syndrome was seen in a total of 1(2%) that is in 1(3.3%) primi and in none of the multigravida.

A total of 7(14%) Newborn babies were required admission in NICU, that is 6 babies born to primi gravidas and 1(5%) baby born to multigravida.

All admitted newborn babies were discharged on 1st PND except one baby who developed MAS (HIE I) treated and discharged on 5th PND.

Table 15

Outcome of Induction

Out come	PRIMI		MULTI		TOTAL	TOTAL
	No	%	No	%	No	%
Success	27	90	20	100	47	94
Failure	3	10	0	0	3	6

The success of induction was seen in 27 (90%) of the total 30 primi and 20 multigravida that is a total of 47 (94%) of the study group.

Failed induction was seen in 3 (10.0) of the total 30 primigravida and in none of the multigravida, that is a total of 3(6%) of study group.

Of the 3 primigravida, 1 underwent lower segment cesarean section for fetal distress while 2 primigravida required PGE_2 gel for induction of labour on Day 4, as their Bishop's score were < 6.

DISCUSSION

50 cases admitted in Government Rajaji Hospital, Madurai for confinement were recruited for this study.

Inclusion Criteria :

The patients were induced in this study after they satisfied all the inclusion criteria. In this aspect, this study correlates with **Randomized control trial conducted by Stenlund et al, Department of woman and child health, Karolinska Hospital, Stockholm, Sweden, Oct 1999.**

Age :

In this study, 27 (90%) primi and 17 (25%) multigravida were between the age group of 21-30 years. This study correlates with **randomized controlled trial conducted by Wing et al, Department of Obstetrics and Gynecology, University of Southern California, Los Angels, Oct 2000** in which 88% of the patients were in the age group of 21-30 years.

Gravidity :

Both primi (60%) and multigravida (40%) were included in the study. In this aspect our study correlates with studies done by **Giacalone et al, Department of Obstetrics and Gynecology,**

Hospital Arnaud de villeneuve, University of Montepetlier, Oct 1998.

Treatment Schedule :

In our study, 200 mg mifepristone was given orally on Day 1, Bishop's scores were assessed after 24 hrs, if less than 6 and reactive PHR pattern, 2nd dose of 200 mg mifepristone orally was given. If Bishop's score remained less than 6 after 48 hrs, PGE_2 gel induction was done on Day 4 (0.5mg intracervically) which was repeated 12 hours later if necessary.

In this aspect, our study correlates with **randomized controlled study done by Frydman et al, Department of Obstetrics and Gynecology, Hospital Antoine Beclere, Clormart, France** in which study population received 200 mg of mifepristone on day 1 and 2 of a 4 days observational period with labour induction using prostaglandin planned on Day 4.

Bishop's Score at the start of the study :

In our study, patients with Bishop's score of less than 4 were included in the study group.

In this aspect, our study correlates with the study done by **Elliot et al, Department of obstetrics and Gynecology, University of Edinburh, United Kingdom** in which modified Bishop score of 4 less were included in the study group.

Oxytocin Augmentation :

In our study, 5 (16.7%) Primi and none of the multi gravida, that is a total of 10% required oxytocin for augmentation.

In this aspect, our study correlates with the study done by **Frydmen et al** in which patient who deliveries vaginally needed a much lower amount of oxytocin when mifepristone had been given.

Duration of First and Second stage of labour :

In this study, a total of 87.8% that is 23 (79.2%) primi and 20 multi (100%) had a first stage duration of less than 12 hrs. The mean duration of first stage in primi was 9.79 hrs and in multi was 6.98 hours.

In this study, a total of 98% that is 28 (96.5%) primi and 20 (100%) multigravida had second stage duration less than 30 minutes. The mean duration of second stage in primi was 16.06 minutes and in multi was 10.78 minutes.

The mean duration of first and second stage was less in multigravida.

These results are consistent with the **normal WHO standards**.

Induction and Delivery Interval :

In this study, mean induction delivery interval was 18.41 hrs. The mean induction delivery interval in primi was 23.11hrs and in multi was 11.48 hrs.

Parity influenced the likelihood of vaginal delivery within 48 hours.

According to the **randomized controlled trial conducted by Wing et al,** mean induction delivery interval was 26.8 $\pm$ 11 hours. 87.5% women who received mifepristone delivered vaginally within 48 hrs. In our study 96.3%. Women delivered vaginally within 48 hrs.

Mode of delivery :

In our study, the incidence of spontaneous vaginal delivery was 88% that is in 24 (80%) primi and 20 (100%) multigravida.

In our study, the instrumental delivery rate was 10% and LSCS rate was 4% which was not statistically significant and in this aspect our study is consistent with Wing DA et al study.

Intrapartum Complications :

In our study, uterine contractility abnormalities like hypertonus, hyperstimulation or tachysystole were not encountered with.

This is in contrast to study conducted by **Giacalone et al, Department of obstetrics and gynecology University of montpellier, July 2001** in which mifepristone treated group had higher rates of hyperstimulation and tachysystole.

A total of 14%, that is 6 primi (20%) and 1(5%) multigravida had FHR abnormalities in our study. This is consistent with study conducted by Wing DA et al in which abnormal FHR pattern were found in 18.6% of the study group.

In our study, a total of 10%, that is 5 (16.6%) primi had thin meconium stained liquor and 1(3.3%) primi had thick meconium stained liquor. But none of the multi had meconium stained liquor. This is consistent with study conducted by Wing et al in which 16.5% infants from mifepristone group had MSAF.

Maternal Complications :

In our study, none of our study population had major complications like rupture uterus, chorioamnionitis, puerperal sepsis, post partum hemorrhage.

A total of 6% study population had minor complications like vomiting and fever.

In this aspect our study consistent with the study conducted by Stenlund et al, Karolinska Hospital, Stockholm, Oct 1999.

Neonatal Outcome :

In our study, a total of 7 (14%) new born babies required admission in NICU. Of the 7 babies one baby had meconium aspiration syndrome and HIE stage I, baby was treated and discharged on V PND. Remaining six babies were admitted for Birth asphyxia. All babies were recovered and discharged on II PND.

None of the babies had neonatal convulsions, icterus or sepsis and perinatal mortality was nil.

In this aspect, our study is consistent with study conducted by **Wing DA et al,** in which no statistically significant difference in

neonatal outcomes between mifepristone treated group and control (placebo) group.

Outcome of Induction :

In our study, none of the study population underwent LSCS for failed induction.

Only 1(2%) primi underwent LSCS for fetal distress out of 50 patients, 2 (4%) primigravida had unfavourable. Bishop's score after 48hrs and required induction with PGE2 gel on Day 4. A total of 93.6% delivered within 48 hrs.

In the study conducted by Wing et al, 87.6% of mifepristone treated group delivered within 48 hours. There was no statistically significant increase in caesarean section rate.

SUMMARY

The efficacy of oral mifepristone as an induction agent is assessed in our study. 50 patients admitted in Government Rajaji Hospital, Madurai for safe confinement, who needed induction, were included for this study. 50 patients satisfying the inclusion criteria for induction of labour were given 200 mg of mifepristone on Day 1 and Day 2 of 4 days observational period. After 24 hrs, Bishop's scores were reassessed, if Bishop's score were more than 6, augmentation with oxytocin was done. If the Bishop's score were remained unfavourable after 48 hrs induction with PGE2 gel was done on Day 4, after ensuring the Reactive FHR pattern. This study documents the success of induction, details of parturition, maternal complications, and neonatal outcome and meticulously the details of the results analysed. The following are the summary of this study.

1. Majority of the patients belonging to this study group were in the age group of 21-30 years (88%) only 12% belonged to the age group of 18-20 years.
2. Analysis with regards to the parity showed that 60% of the study group were primi gravida and 40% were multigravida.

3. With regards to the indications for induction, post dated pregnancy formed the majority (90%) and the other indication was preeclampsia (10%).

4. Majority of the patients in our study had a Bishop's score of 0 to 2 (84%) at the beginning of the induction. Critical analysis among primi and multigravida showed that the distribution was almost equal (86.7% primi vs 80% multi).

5. Analysing the number of doses of mifepristone needed to produce mature cervices (Bishop's score >6) or delivery. With single dose a total of 80%, that is 70% primi and 95% multi either delivered or having mature cervices (Bishop score > 6) showing that the drug mifepristone is a effective inducing agent. Only 20%, that is 30% primi and 5% multi gravida needed second dose.

6. Anaysing the need for oxytocin augmentation. Only 16.7% of the primigravida required oxytocin for augmentation. None of multigravida required oxytocin for augmentation ; mifepristone reduces the need for oxytocin augmentation.

7. Analysing the requirement of PGE2 gel for cervical ripening on Day 4, only 2 primigravida (6.6%) had unfavourable

Bishop score (Bishop's score < 6) after 48 hrs and required PGE2 gel induction on Day 4. But none of the multigravida had unfavourable Bishop's score at the end of 48 hrs, showing that mifepristone is a effective cervical ripening agent.

8. Analysis of duration of first stage of labour revealed that 87.8% patient had first stage duration of less than 12 hours and all of the patients delivered within 16 hours, showing that the drug shortens the first stage duration of labour in the majority (87.8%). On critical analysis, 79.2% primi and 100% multigravida had first stage duration of less than 12 hours, showing that parity influenced the likelihood of vaginal delivery.

9. The duration of second stage was less than 30 minutes in 98% of patients. On critical evaluation almost all multigravida and 96.5% primigravida had second stage duration of less than 30 minutes. The mean second stage duration in primi and multi gravida being 16.06 minute and 10.78 minutes respectively.

10. With regards to the induction delivery interval (after subtracting the failure cases) 91.5% patients delivered within 36 hrs of induction. Only 4 primi (19.7%) but none of the multigravida delivered after 36 hrs of induction. The mean induction delivery interval was 18.61 hrs. The mean induction is delivery interval in primi was 23.7 hrs and in multigravida was 11.48 hrs. Therefore induction delivery interval was shorter in multigravida (p=0.001).

11. Intrapartum complications : None of the study population had uterine contractility abnormalities, though 14% patients showed FHR abnormalities, and 10% had thin meconium stained liquor 2% had thick meconium stained liquor, the neonatal outcome was good.

12. Unassisted vaginal delivery occurred in 100% multigravida and 80% multigravida. Only 5 (16.6%) primigravida required instrumental delivery (outlet forceps) and 1(3.3%) primigravida underwent LSCS for foetal distress showing that the drug is very effective in minimizing the ceasarean section rates to a base minimum.

13. There were no major maternal complications like rupture uterus, post partum hemorrhage, and puerperal sepsis both in the primi and multigravida showing that safety and efficacy of this regime. Only 6% patients had minor complications like nausea, vomiting and fever.

14. Critical evaluation of the neonatal outcome in our study revealed no statistical difference in the mean birth weight of the baby born (mean birth was 2.9 kgs and 2.81kgs in multi gravida) In 10% of the new borns, the 5 minutes Apgar scores were less than 7/10, all 4 babies were admitted in NICU and observed for 12 hours and discharged after 12 hours. Apart from these babies, two newborns, one for VLBW (B.Wt – 1.8kg) and one for MAS (meconium aspiration syndrome) were admitted in the NICU. The new born who had MAS developed HIE-I and treated in NICU, recovered and discharged on Vth PND. Neonatal mortality was NIL and none of the babies had septicemia.

15. The outcome of induction in this study reveals that the drug was successful in 94% of the cases. Only 2 primigravida required PGE2 gel induction on Day 4 and 1 primi gravida underwent LSCS for foetal distress showing that mifepristone is a safe and effective drug for preinduction cervical ripening at term in patients with unfavourable cervices.

CONCLUSION

Our study reveals that oral mifepristone is a very safe and effective drug for the induction of labour. It has an added advantage of the case of administration (oral). This drug effectively reduces the need for augmentation of labour in almost three fourth of the patients and with overall success rate of 94%.

The drug shortens the duration of the labour with absolutely no major maternal complications and with absolutely safe neonatal outcome. Compare to overall hospital standards, when the drug is used, lower segment caesarean rates were minimal thereby showing that mifepristone is a safe and orally effective agent for induction of labour at term in patients with unfavourable cervices, but more studies are needed.

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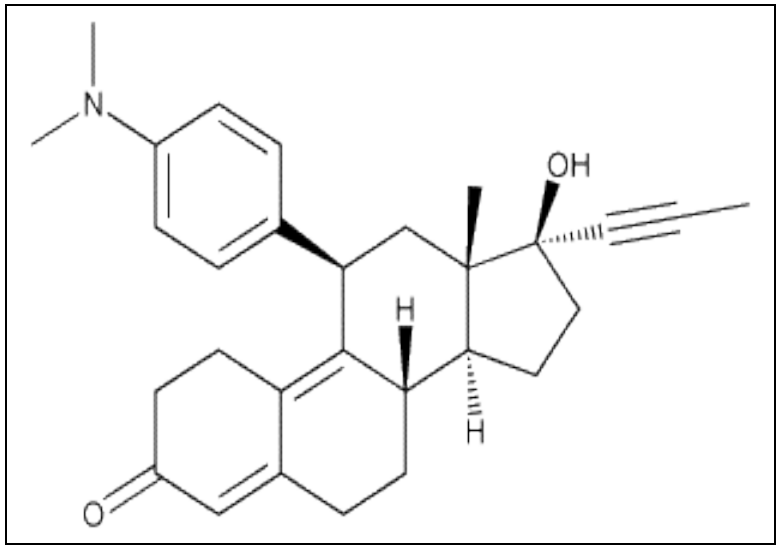
STRUCTURE OF MIFEPRISTONE



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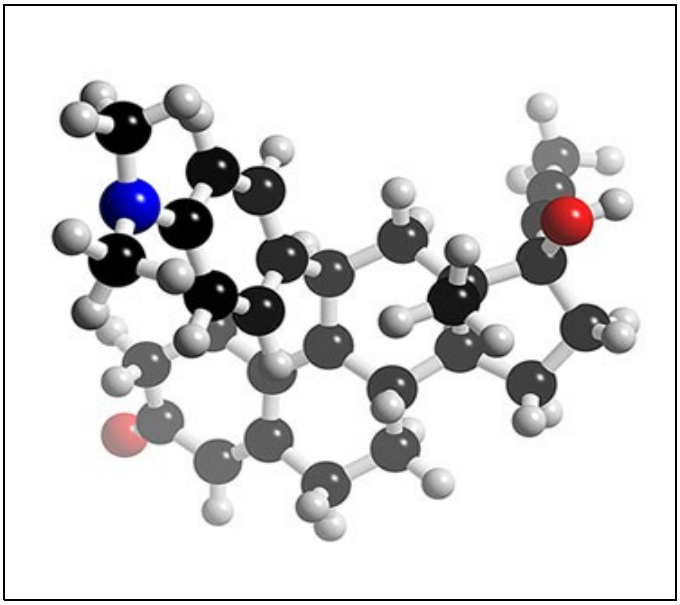

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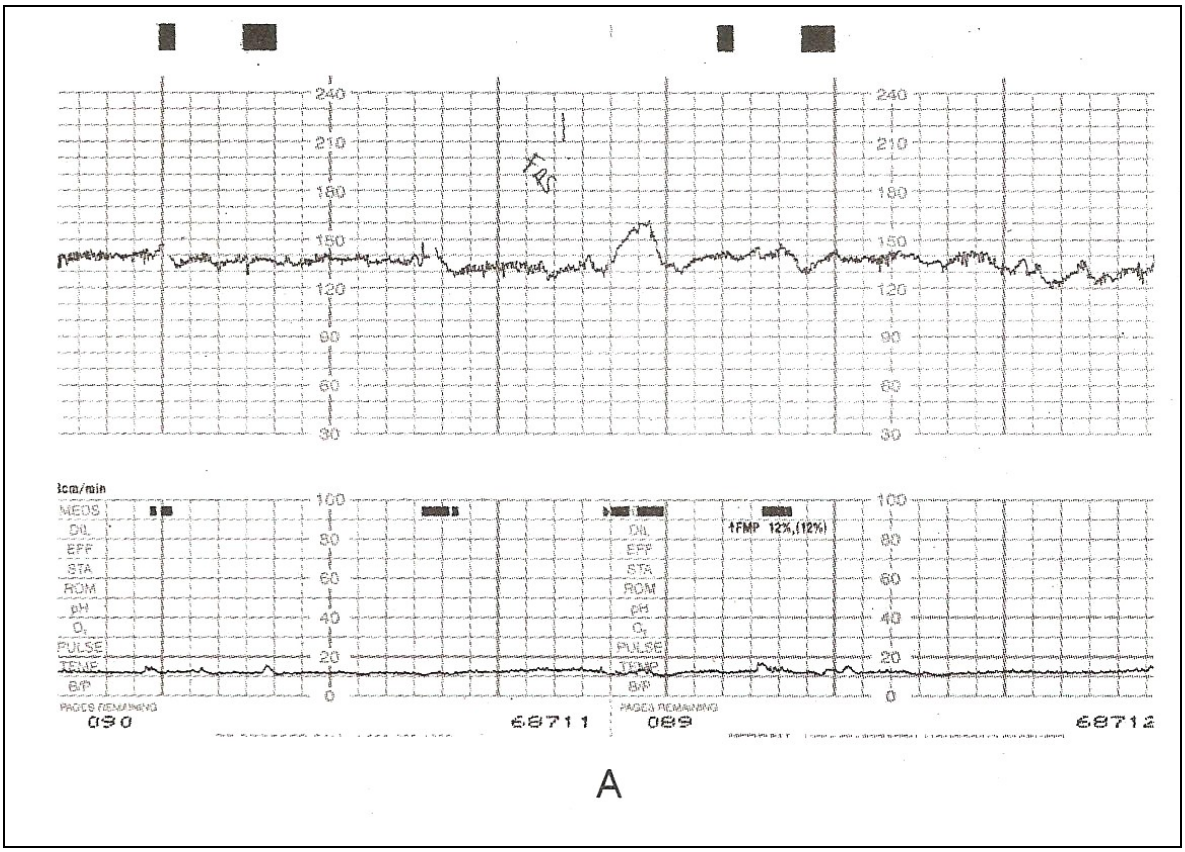

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MIFEPRISTONE TABLETS

ABBREVIATIONS

NICU	NEONATAL INTENSIVE CARE UNIT
MSAF	MECONIUM STAINED AMNIOTIC FLUID
MAS	MECONIUM ASPIRATION SYNDROME
HIE	HYPOXIC ISCHEMIC ENCEPHALOPATHY
NST	NON STESS TEST
WKS	WEEKS
MIN	MINUTES
KGS	KILOGRAMS
MG	MILLI GRAMS
FHRAb	FETAL HEART RATE ABNORMALITY

PROFORMA

MIFEPRISTONE (RU 486) IN INDUCTION OF LABOUR.

Name :

Age :

IP No :

Socio economic status :

Obstetric Code :

Booked /unbooked :

Last mestural period :

Expected date of delivery :

HISTORY:

PAST HISTORY:

H/o Diabetes / Hypertension / Congenital or Rheumatic Heart Disease/

H/o Drug Intake like anti coagulants / H/o Tuberculosis (or) chronic lung disease H/o epilepsy / H/o Steroid therapy.

H/o Surgeries

PERSONNEL HISTORY:

H/o Smoking

MENSTRUAL HISTORY:

H/o Regular Cycles

MARITAL HISTORY :

Married since Yrs.

H/o Consanguinity

OBSTETRIC HISTORY

GENERAL EXAMINATION

Height

Weight

Anemic / not

Afebrile / febrile

Pedel oedema present / absent

Pulse rate:

Blood pressure

Cardio vascular system

Respiratory system:

Abdominal Examination

Vaginal Examination

Bishop's score (modified) at the time of Induction. :

BASIC INVESTIGATIONS

Hb%

Urine alb

Sugar

Deposits

Blood grouping Rh typing

Blood sugar

Urea

Sr. creatinine

Obstetric Scan & Biophysical Profile

INDICATION FOR INDUCTION:

DATE AND TIME OF MIFEPRISTONE (200 MG ORALLY) ADMINISTRATION

DOSE	DATE	TIME
IST Dose		
IInd Dose		

BISHOP SCORE AFTER 24HRS & 48 HOURS

Bishop score after 24 hr	After 48 hrs

Oxytoxin Augmentation : Needed / not

Dose and duration

Duration of first stage _____ in hours

Duration of second stage _____in minutes

Mode of delivery Labour natural / Instrumental delivery /LSCS

Induction delivery Interval:

Intra partum complications:

Maternal Complications:

Neonatal outcome:

Birth weight

Apgar 1’

5’

If admitted in NICU, Outcome of the newborn.